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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/852,666	05/07/97	CHADA	K UMD-1.0-037C

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HM12/0224

EXAMINER
SRIVASTAVA, D

ART UNIT	PAPER NUMBER
1652	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/852,666	Applicant(s) Chada et al.
	Examiner Devesh Srivastava, Ph.D.	Group Art Unit 1652

Responsive to communication(s) filed on Jan 29, 1999

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

Claim(s) 1-15, 17-28, and 30-40 is/are pending in the application.

Of the above, claim(s) 1-5, 13-15, 20-22, 26-28, and 33-40 is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 6-12, 17-19, 23-25, and 30-32 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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Response to Amendment

1. Applicant's amendment, filed 2/4/99, has been entered and fully considered. Claims 16 and 29 have been cancelled by Applicant, claims 1-5, 13-15, 20-22, 26-28 and 33-40 remain withdrawn as being drawn to non-elected inventions, the restriction requirement having been made final in Paper No. 8, and claims 6-12, 17-19, 23-25 and 30-32 are pending.

Objections/Rejections Withdrawn

2. In light of filing of a new declaration, the previous objection to the declaration is withdrawn.
3. In light of filing of a new Abstract, the previous objection to the Specification is withdrawn.
4. In light of cancellation of claims 16 and 29 and amendments to claims 6 and 23, the previous rejection of claims 6-12, 16-19, 23-25 and 29-32 under 35 U.S.C. 112, second paragraph is withdrawn.

Response to Arguments

5. Claims 6-12, 17-19, 23-25 and 30-32 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the prior Office Action, Paper No. 8.
6. Applicants traverse the above rejection with the following arguments. With respect to claims 23-25 and 30-32, Applicants argue that (1) genetic mutations of HMGI-C or HMGI(Y) in humans result in various solid mesenchymal tumors (page 8, lines 6-16); (2) results obtained from

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a HMGI-C knockout mouse demonstrate a role for HMGI proteins in normal and pathological development in the mouse system (page 8, lines 17-26 and page 9, lines 1-6); **(3)** some human lipomas have been linked to rearrangement at chromosome 12m bands q14-15 where HMGI-C is mapped and this suggests a role for HMGI-C in adipogenesis and mesenchymal differentiation (page 9, lines 10-20); **(4)** disruption of HMGI-C in mice produces small stature and disproportionately less body fat and the mouse HMGI-C maps to a region syntenic to human 12q14-15, thus linking HMGI-C to lipomas (page 9, lines 21-28 and page 10, lines 1-2); **(5)** the pygmy mouse mutant phenotype arises from inactivation of HMGI-C (page 10, lines 3-11); **(6)** HMGI-C and HMGI(Y) are expressed during embryogenesis and are regulated during cell cycle (page 10, lines 11-16); **(7)** an array of mesenchymal tumors is characterized by rearrangements of chromosomal bands 12q13-15 or 6p21-23 and that HMGI expression is activated in differentiated adipocytes following translocations of 12q13-15 or 6p21-23 in human lipomas (page 10, lines 17-26); and **(8)** uterine leiomyomata is characterized by rearrangement of chromosome 12 in bands q14-q15 and that HMGI-C, which maps to a YAC spanning chromosome 12 translocation breakpoints identified in uterine leiomyoma, pulmonary chondroid hamartoma and lipoma, is disrupted in lipomas and that tanslocation breakpoints in uterine leiomyomata localize 10 to > 100 kb upstream of HMGI-C (page 11, full page). Applicants further argue that the law doesn't require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 U.S.C. 112, first paragraph, especially when essential elements are well-known in the art (page 12, lines 3-17) and that a patent application need not describe the limitations of a claimed process

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in such a way that those skilled in the art would recognize that applicant invented the claimed process (page 12, lines 18-22).

7. Applicant's arguments filed 2/4/99 have been fully considered but they are not persuasive.

First, Applicants arguments have been directed to situations encompassing growth and development of adipose tissue, which, according to the arguments, also encompass abnormal (cancer or tumor) growth. None of the arguments are directed to an actual method for regulating such processes, which is what was claimed in claims 23-25 and 30-32. Further, no arguments have been directed to claimed methods of treating obesity (claims 6-12 and 17-19).

Second, while it may be true that some human lipomas have been linked to rearrangement at chromosome 12m bands q14-15 where HMGI-C is mapped, that this would "*suggest a role for HMGI-C in adipogenesis*" and that HMGI expression is activated in human lipomas (items (3) and (7) above), Applicants have failed to demonstrate how this relates to the claimed invention of methods of regulating growth and development of adipose tissue. It is unclear to the Examiner how naturally occurring genetic defects in humans correspond to the claimed invention, which is directed to methods of treating obesity (claims 6-12 and 17-19) or to methods of regulating growth and development of adipose tissue (claims 23-25 and 30-32) in a mammal.

Third, the murine knockout studies (item (4) above) are also not directed to the claimed invention especially when considering that a mouse does not encompass the entire genus of mammal, which, according to the specification may be human or rodent (page 11, lines 18-19) and that a decrease in stature by homologous recombination does not equate to a treatment of

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obesity or regulation of growth and development of adipose tissue. Further, homologous recombination is not a method by which treatment of obesity or regulation of growth and development of adipose tissue is to be accomplished, as disclosed in the specification. As stated in the previous Office Action, claims 6-12 and 17-19 (claim 16 was cancelled in Paper No. 9) recite methods for treating obesity in mammals and claims 23-25 and 30-32 (claim 29 was cancelled in Paper No. 9) recite methods for regulating growth and development of adipose tissue. The specification discloses: "*The reduction in biological activity of HMGI genes may be achieved by inhibiting the DNA-binding activity of HMGI genes which may be carried out by administering to the mammal a therapeutically effective amount of netropsin, distamycin A or Hoechst 33258 (bisbenzimide).*" (page 11, lines 13-16). Since these drugs are not known in the art to reduce the *in vivo* activity of HMGI proteins, it can not be predicted if such a reduction would occur. Applicants have failed to teach the composition in which any of the three drugs will be administered, the frequency of administration or the need for coincidental changes in behaviour including diet and exercise or the effect of confounding factors such as diabetes especially when such method of treatment is not known in the art of treating obesity (emphasis added). Where a teaching is absent from the art, Applicant must teach how to use the invention. The specification further discloses: "*The reduction in biological activity of HMGI genes may be achieved by inhibiting the expression of HMGI genes which may be carried out by administering to the mammal a therapeutically effective amount of an oligonucleotide which has*

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a nucleotide sequence complementary to at least a portion of the mRNA of the HMGI gene.”

(page 11, lines 9-13). This is clearly not the same as homologous recombination.

With respect to claims 6-12 and 17-19, Marx states that “*Few medical problems have proved to be more intractable than obesity*” (page 1477, column 1, , lines 1-2) and Rink states “*...much remains to be done*” towards therapeutic approaches to obesity (page 407, column 2, line 12). **This clearly demonstrates that methods of treating obesity are not enabled** (emphasis added). Where teachings are absent in the art, Applicant must teach how to use the invention.

With respect to antisense oligonucleotide approaches to reduce biological activity of HMGI genes, Branch states “*the antisense field has been turned on its head by the discovery of ‘non-antisense’ effects, which occur when a nucleic acid drug acts on some molecule other than its intended target*” and this “*unpredictability confounds research applications of nucleic acid reagents.*” (page 45, column 2, lines 3-7 and 13-15). Branch further states “*internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules.*” (page 45, column 3, lines 1-5). The latter point illustrates the need for antisense oligonucleotides that are complementary to exposed regions of target RNA. It is unclear if the disclosed antisense oligonucleotides are complementary to exposed regions of target RNA. This clearly demonstrates that antisense approaches to reducing biological activity of HMGI genes is not enabled. Where teachings are absent in the art, Applicant must teach how to use the invention.

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With respect to claims 23-25 and 30-32, Guerre-Millo et al. state “*Although major progress has been made into clarifying the basic role of transcription factors in adipocyte differentiation, major challenges lie ahead before this can be extrapolated to the human situation.*” (page 1530, column 1, lines 20-23) and Auwerx et al. state “*...studies should be designed to test whether results obtained using animal models and in vitro cell culture systems can be extrapolated to the human situation and eventually applied in medical practice. Although enormous progress has been made regarding the role which transcription factors play in adipocyte differentiation, major challenges lie ahead.*” (page 350, column 2, lines 1-7).

The art, as referenced above, suggest that there is much more to be done before effective regulation of growth and development of adipose tissue (adipogenesis) can be performed. Further, given the unpredictability in the art, there is also a lack of a working example in the specification. Specifically, **there is no example of a reduction in biological activity of an HMGI protein in a mammal that is produced by either of the disclosed methods** (emphasis added).

Finally, it is unclear to the Examiner how argument items (1), (2), (5), (6) and (8) relate to the claimed invention of methods of treating obesity and regulating growth and development of adipose tissue.

The Examiner has established in the previous rejection and reiterated above that methods of treating obesity and methods of regulating growth and development of adipose tissue are not well known in the art, although Applicants assume that the necessary teachings exist in the art

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(page 12, lines 3-6). In fact, the Examiner has established that approaches to treating obesity or regulating growth and development of adipose tissue, even now, are not enabled in the art.

Applicants have clearly failed to demonstrate that their methods are enabled, especially when the art teaches otherwise. Therefore, Applicants have failed to teach how to use their claimed invention.

Conclusion

8. No claim is allowed.
9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Devesh Srivastava, Ph.D. whose telephone number is (703) 305-0775. The

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examiner can normally be reached on Monday-Thursday from 8:00 am to 5:30 pm and alternate Fridays from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Wax, can be reached on (703) 308-4216. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Devesh Srivastava, Ph.D.
Patent Examiner


Robert A. Wax
Supervisory Patent Examiner
Technology Center 1600